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EFFECTS OF A 13-WEEK CHLOROPENTAFLUOROBENZENE INHALATION EXPOSURE OF FISCHER 344 RATS AND B6C3F1 MICE

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TECHNICAL REVIEW AND APPROVAL

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The experiments reported herein were conducted according to the "Guide for the Care and Use of Laboratory Animals," Institute of Laboratory Animal Resources, National Research Council.

This report has been reviewed by the Office of Public Affairs (PA) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This technical report has been reviewed and is approved for publication.

FOR THE COMMANDER

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Chloropentafluorobenzene (CPFB) has been identified as a candidate uptake simulant for nonpersistent chemical warfare agents. Acute toxicity studies have shown that CPFB has limited adverse effects on laboratory animals. A 21-day inhalation study of rats and mice to 2.5, 0.8, and 0.25 mg CPFB/L resulted in reduced weight gain in the high concentration male and female rats only and identified the liver as a potential target organ. In evaluations for its potential to induce chromosomal damage following inhalation exposure, CPFB did not alter the rate of bone marrow cellular proliferation. Assessment of micronucleated polychromatic erythrocyte and nonmochromatic erythrocyte populations during the inhalation exposure indicated a general absence of genotoxic activity. This multiconcentration inhalation study was designed to detect a no-observable-effect level associated with repeated exposure to CPFB. Male and female rats and mice were exposed to 250, 50, or 10 mg CPFB/m^3 (0.25, 0.05, or 0.01 mg CPFB/L) for 13 weeks. No effects on body weight, clinical chemistries, or mortality were noted at the conclusion of the study.

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PREFACE

This is one of a series of technical reports describing results of experimental laboratory programs conducted in the Toxic Hazards Research Unit, NSI Technology Services Corporation, Environmental Sciences. This document serves as a final report on selected toxicity studies of chloropentafluorobenzene (CPFB). The research described in this report began in February 1989 and was completed in October 1990. It was performed under U.S. Air Force Contract No. F33615-85-C-0532. Lt. Col. Michael B. Ballinger and Maj. James N. McDougal served as Contract Technical Monitors for the U.S. Air Force, Harry G. Armstrong Aerospace Medical Research Laboratory.

The animals used in this study were handled in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals, prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health and Human Services, National Institute of Health Publication #86-23, 1985, and the Animal Welfare Act of 1966, as amended.

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ABBREVIATIONS

ALKP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
C	Celsius
CPFB	Chloropentafluorobenzene
dL	Deciliter
F-344	Fischer 344 rats
g	Gram
h	Hour
IU	International unit
kg	Kilogram
L	Liter
LC_{50}	Lethal concentration, 50%
LD_{50}	Lethal dose, 50%
m^3	Cubic meter
mg	Milligram
mm	Millimeter
mmol	Millimole
N	Number
p	Probability
SEM	Standard error of the mean
SGOT	Serum glutamic-oxalacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase

SECTION 1

INTRODUCTION

Chloropentafluorobenzene (CPFB) is a candidate material for use as a chemical warfare simulant by the military for training purposes. Troops wearing chemical defense gear will be exposed to training environments containing realistic concentrations of simulant vapor and aerosol in order to assess both the training proficiency of the personnel and mask efficacy. Preliminary screening has indicated that CPFB provides good detectability for biological monitoring, desirable partitioning in biological tissues, acceptable physical properties, and relative acute biological inertness (Jepson et al., 1985). The primary irritation hazard, sensitization potential, and acute inhalation toxicity of CPFB have been evaluated in this laboratory (Kinkead et al., 1987). CPFB demonstrated no potential for skin sensitization in guinea pigs; however, it did produce mild skin and conjunctival irritation in rabbits. Short-term exposure to CPFB vapor posed no serious hazard by the inhalation route as all rats survived a 4-h exposure of 4.84 mg/L. The results of a 21-day inhalation study at concentrations of 2.50, 0.80, and 0.25 mg CPFB/L (2500, 800, and 250 mg/m^3) were reported by Kinkead et al. (1990). Mean body weights of male and female rats exposed to 2.50 mg CPFB/L were depressed significantly during the last two weeks of the three-week study. Clinical effects included significant increases in liver/body weight ratios in both sexes of rats and mice. The greatest increase over control values (71%) occurred in female mice. Histopathologic results of the 21-day inhalation study indicated significant hepatocytomegaly in both male and female mice exposed at 2.5 mg CPFB/L. Hepatocellular necrosis was seen in at least 67% of the test mice, but also was noted in 50% of the control mice. Hyaline droplets were noted in kidneys of all test male rats. It was anticipated that under the conditions of intended use individuals would be exposed to this simulant on a short-term repeated or, in the case of instructors, reoccurring basis. Therefore, it was necessary to determine the effects of repeated inhalation exposures to this material.

This multiconcentration inhalation study was designed to detect a no-observable-effect level associated with repeated exposure to CPFB for 13 weeks. The study included mice that were maintained for six-months postexposure to determine if treatment-related effects were reversible.

Both the rat and mouse were selected as test species for the 13-week repeated inhalation study because of the effects seen following the 21-day inhalation study. The inhalation route was chosen because it is the most likely route of potential human exposure in the manufacture and use of CPFB. The species and numbers of animals per group were selected to conform with the Environmental Protection Agency Health Effects Guidelines (1985) and to allow for significant statistical evaluation

of the results. Existing alternative methods to animal testing were inadequate for this study, which was designed to investigate the effect of repeated treatment on intact mammalian systems.

A review of the acute toxicity data available on CPFB revealed that the acute oral toxicity of this compound had never been established. To provide a complete hazard assessment it was necessary to include this information. The Fischer 344 (F-344) rat was selected as the test species for this evaluation.

SECTION 2

MATERIALS AND METHODS

TEST AGENT

The CPFB used in this study was purchased from Aldrich Chemical Co., Milwaukee, WI. A Material Safety Data Sheet was not available from the manufacturer. The physical properties of CPFB are shown in Table 1.

TABLE 1. PHYSICAL PROPERTIES OF CPFB

Chemical Formula	C_6ClF_5
Molecular Weight	202
Boiling Point (°C)	122
Density (g/mL)	1.568
Vapor Pressure (mmHg, 25 °C)	14.1
CAS No.	344-07-0

Samples were taken for analysis from each of five supply containers. An infrared spectrum of CPFB was generated using a Beckman Acculab 4 (Beckman Instruments, Inc., Fullerton, CA) infrared spectrophotometer. Results of this analysis indicated no significant differences between the samples of stock material.

ANIMALS

Upon receipt from Charles River Breeding Labs (Kingston, NY), male and female F-344 rats, six weeks of age, and male and female B6C3F1 mice, six weeks of age, were quality control tested and found to be in acceptable health. They were group-housed (two to three per cage) in clear plastic cages with wood-chip bedding prior to the study. The rats and mice (nine weeks of age at initial exposure) were individually housed and assigned to specific exposure cage locations during the study. The exposure cages were rotated daily in a clockwise manner (moving one position) within the 690-L inhalation chambers to compensate for any possible variation in chamber exposure conditions. Water and feed (Purina Formulab #5008) were available ad libitum except during the inhalation exposure period when food was removed and when the animals were fasted for 10 h prior to sacrifice. Ambient temperatures were maintained at 21 to 25 °C and the light/dark cycle was set as 12-h intervals (light cycle starting at 0700 h).

Fischer 344 rats for the acute oral toxicity study, also purchased from Charles River Breeding Labs, were quality control tested and found to be in acceptable health. The animals were group

housed in clear plastic cages with wood-chip bedding throughout the study. Food, water, and ambient conditions were similar to those of the inhalation study mentioned above.

ORAL TOXICITY

Sixteen hours prior to the administration of the oral dose, five male and five female F-344 rats, nine weeks of age, were fasted. Each rat was weighed just prior to oral gavage dosing and a 5-g/kg dose of neat CPFB was administered. Surviving rats were weighed at 1, 2, 3, 7, 10, and 14 days posttreatment and signs of toxicity recorded. On the 14th day posttreatment, the rats were sacrificed and gross pathology performed. Tissues were harvested for histopathologic examination.

INHALATION TOXICITY

Generation and Analysis of Exposure Atmospheres

CPFB vapor for the two highest exposure concentrations was generated by metering air through a glass fritted dispersion tube immersed in a gas-washing bottle that contained liquid CPFB (Figure 1). The test atmosphere in the low exposure concentration chamber was generated using a midget impinger. The liquid levels in the reservoirs were maintained using a polystaltic pump. The vaporized CPFB was delivered into the chamber through a stainless steel tube where it was mixed countercurrently with the chamber air supply. Concentration was controlled by adjusting the volume of air passing through the liquid reservoir. The chamber atmospheres were monitored continuously using a Miran 1A infrared analyzer (Foxboro, S. Norwalk, CT). Because water vapor interfered at the wavelength scanned, the Miran was not used as a primary indicator of concentration, but as a means to monitor fluctuations in chamber concentration. Gas chromatography (Varian 1200, Varian Associates, Palo Alto, CA) was used as the primary method for measuring CPFB concentration in the exposure chambers. Samples were taken every 5 min, cycling from the control chamber through the high concentration chamber, resulting in an analysis of each chamber every 20 min.

Exposure Regimen and Response Assessment

Eight male and eight female F-344 rats and 12 male and 12 female B6C3F1 mice were placed in four 690-L inhalation chambers and exposed for 6 h/day, 5 days/week, for 13 weeks (65 exposures over a 90-day test period) to either air only, 10, 50, or 250 mg CPFB/m^3. Records were maintained for body weights, signs of toxicity, and mortality. All rats and eight of the 12 mice per group were sacrificed following the final exposure. Four mice per group were maintained for six months postexposure. Euthanasia was accomplished via halothane inhalation overdose. At sacrifice, gross pathology was performed on all animals, and tissues (Table 2) were harvested for histopathologic examination. Wet tissue weights were determined on adrenals, brain, heart, kidneys, liver, lungs, ovaries, spleen, testes, and thymus. Tissues for histopathologic examination were fixed in 10%

neutral-buffered formalin, trimmed, and further processed via routine methods for hematoxylin-eosin-stained, paraffin-embedded sections (Luna, 1968).

Additionally, blood was drawn for hematology (Table 3) and clinical chemistry (Table 4) assays. Erythrocytes were enumerated on a Coulter counter (Coulter Electronics, Hialeah, FL), and sera for clinical chemistry evaluation were assayed on an Ektachem 700XR (Eastman Kodak, Rochester, NY). Selected hematological parameters and absolute leukocyte differentials were determined according to established procedures. Sera were processed according to the procedures in the Ektachem operation manual.

STATISTICAL ANALYSIS

Comparisons of mean body weights were performed using the Multivariate Analysis of Covariance for Repeated Measures Test (Barcikowski, 1983; Dixon, 1985). A two-factorial analysis of variance with multivariate comparisons was used to analyze the hematology, clinical chemistry, and organ weight data.

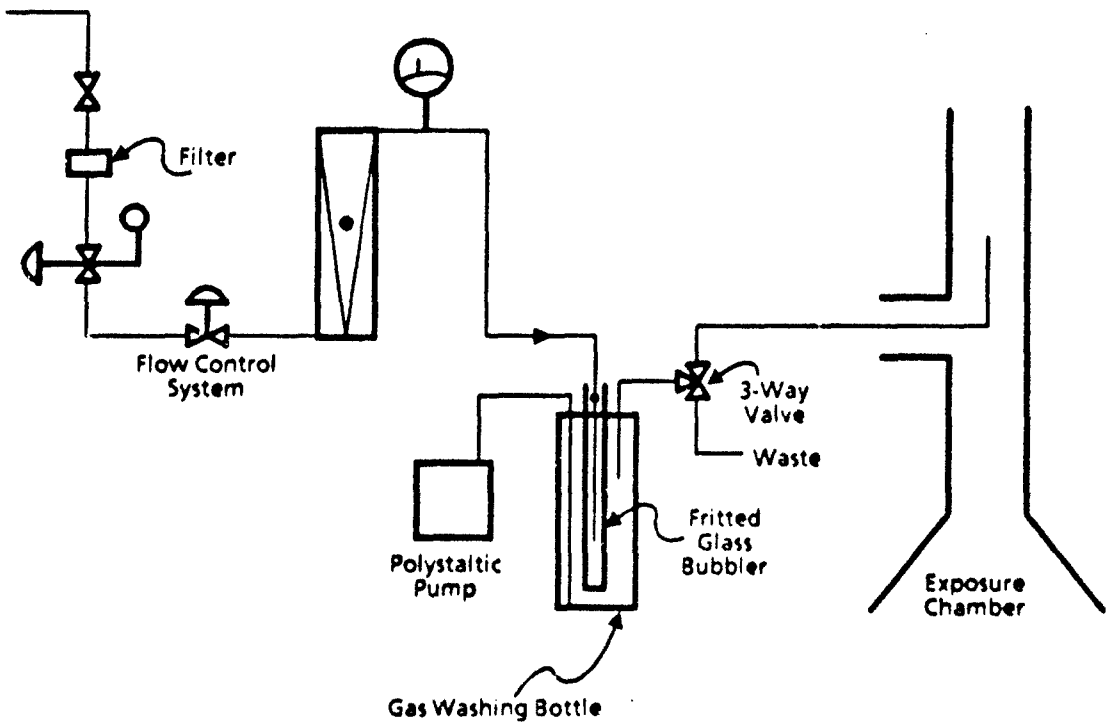

Figure 1. Test Atmosphere Generation System.

TABLE 2. TISSUES HARVESTED FROM CONTROL AND CPFB-EXPOSED F-344 RATS AND B6C3F1 MICE FOR HISTOPATHOLOGIC EXAMINATION

Gross lesions	Thymus
Brain	Kidneys
Lungs	Adrenals
Trachea	Pancreas
Heart	Ovaries/testes
Liver	Nasal turbinates
Spleen	Uterus (females)
Duodenum	Esophagus
Jejunum	Stomach
Ileum	Colon
Urinary bladder	Rectum
Mandibular lymph nodes	Sternum
Mesenteric lymph nodes	Sciatic nerve
Skeletal muscle	Gallbladder (mice)
Tooth (incisor)	Bone (stifle joint to include femur and tibia)

TABLE 3. ASSAYS PERFORMED ON WHOLE BLOOD FROM CONTROL AND CPFB-EXPOSED RATS

Hematocrit
Hemoglobin
Red Blood Cell Count and Indices
Total and Differential Leukocyte Count
Platelet Count

TABLE 4. SERUM CHEMISTRY ASSESSMENTS OF CONTROL AND CPFB-EXPOSED ANIMALS

Rats	
Alanine Aminotransferase (ALT)	Bilirubin
Aspartate Aminotransferase (AST)	Chloride
Alkaline Phosphatase (ALKP)	Calcium
Blood Urea Nitrogen	Sodium
Creatinine	Glucose
Total Protein	Cholesterol
Potassium	Phosphorus
Albumin	Serum Triglyceride
Mice	
Alkaline Phosphatase (ALKP)	Blood Urea Nitrogen
Alanine Aminotransferase (ALT)	Creatinine
Aspartate Aminotransferase (AST)	

SECTION 3

RESULTS

ORAL TOXICITY

Five male and five female F-344 rats were orally dosed with neat CPFB at the limit test-dose level of 5 g/kg. All rats lost consciousness following dosing, then revived by 24 h but appeared lethargic. One male rat died one day after dosing and two female rats died two days posttreatment. By the third day posttreatment all survivors appeared normal. Following an initial weight loss the surviving animals had effectively returned to their initial body weight by seven days posttreatment and then gained at a normal rate during the final week of posttreatment observations. No significant lesions that appeared to be treatment related were found in animals that died spontaneously or were sacrificed 14 days posttreatment.

INHALATION TOXICITY

The specified target concentrations of 250, 50, and 10 mg CPFB/m^3 were maintained during the 13-week exposure period. Chamber daily mean concentrations of the two highest exposure groups were maintained within ± 10% of the target concentrations. Chamber daily mean concentration of the 10-mg CPFB/m^3 chamber was maintained within ± 21% of the desired concentration. Mean concentrations for each exposure chamber, along with the high and low daily mean concentrations, are provided in Table 5.

TABLE 5. ANALYSIS OF CPFB CONCENTRATIONS INHALED BY RATS AND MICE FOR 13 WEEKS

Target Concentration	10 mg/m^3	50 mg/m^3	250 mg/m^3
Mean Concentration, mg/m^3	10.1	50.4	251.4
Standard Deviation	0.7	1.4	4.5
Highest Daily Average, mg/m^3	12.5	54.9	269.8
Lowest Daily Average, mg/m^3	8.3	47.5	240.6

A total of 64 F-344 rats and 96 B6C3F1 mice were included in the 13-week inhalation study. There were no rat deaths resulting from exposure. One female mouse, exposed at 10 mg CPFB/m^3, was found dead following the twenty-ninth exposure day. Examination of this animal determined the cause of death to be leukemia.

No treatment-related effects on mean body weight gains were noted in either male or female rats or female mice during the 13-week study (Figures 2 and 3, and Appendices A through D). The high-level male mouse group had a depression in mean body weights at the conclusion of the study; however, the difference was not statistically significant.

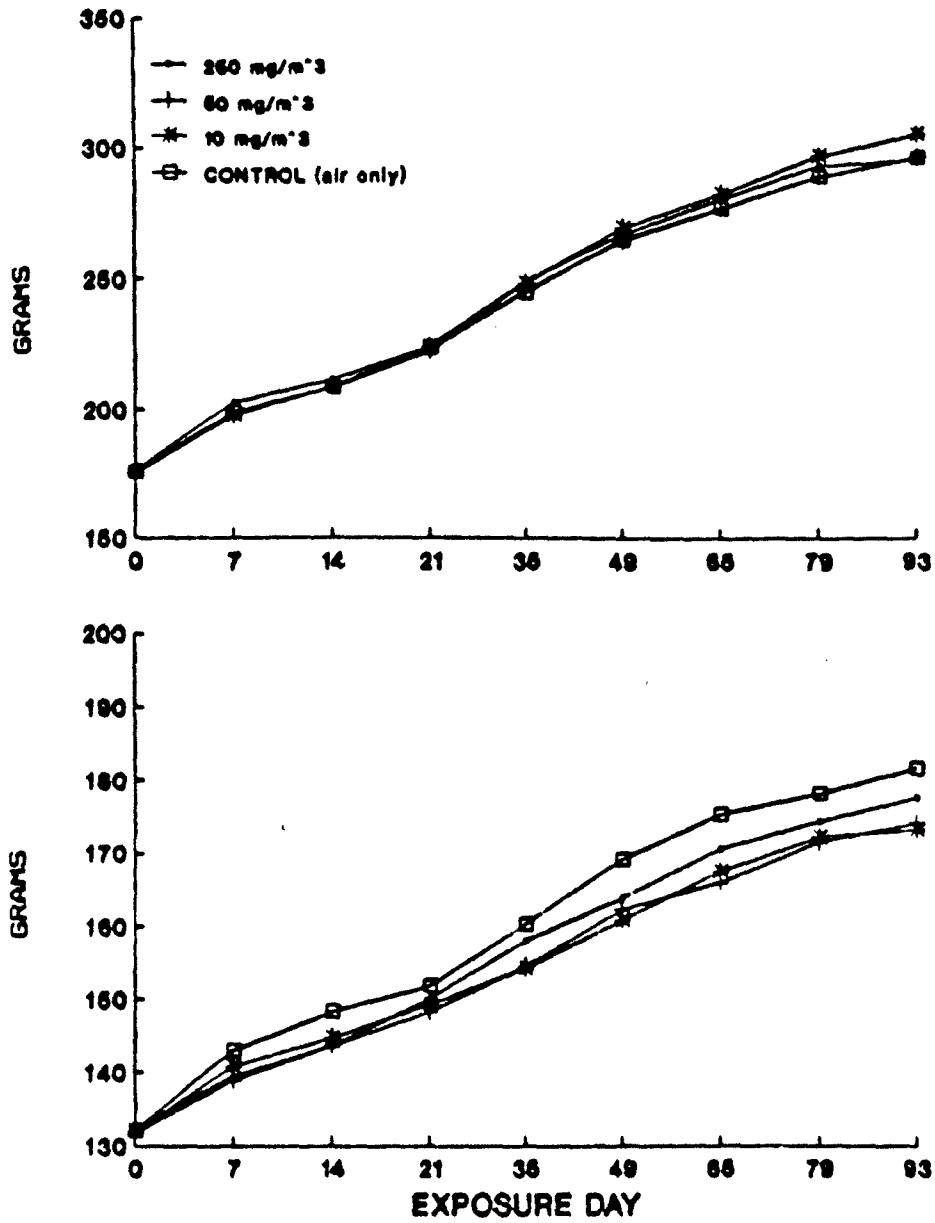

Figure 2. Effect of 13-Week CPFB Inhalation Exposure on Mean Body Weights of F-344 Male (above) and Female Rats (N = 8). There were no statistical differences between treatment groups and controls.

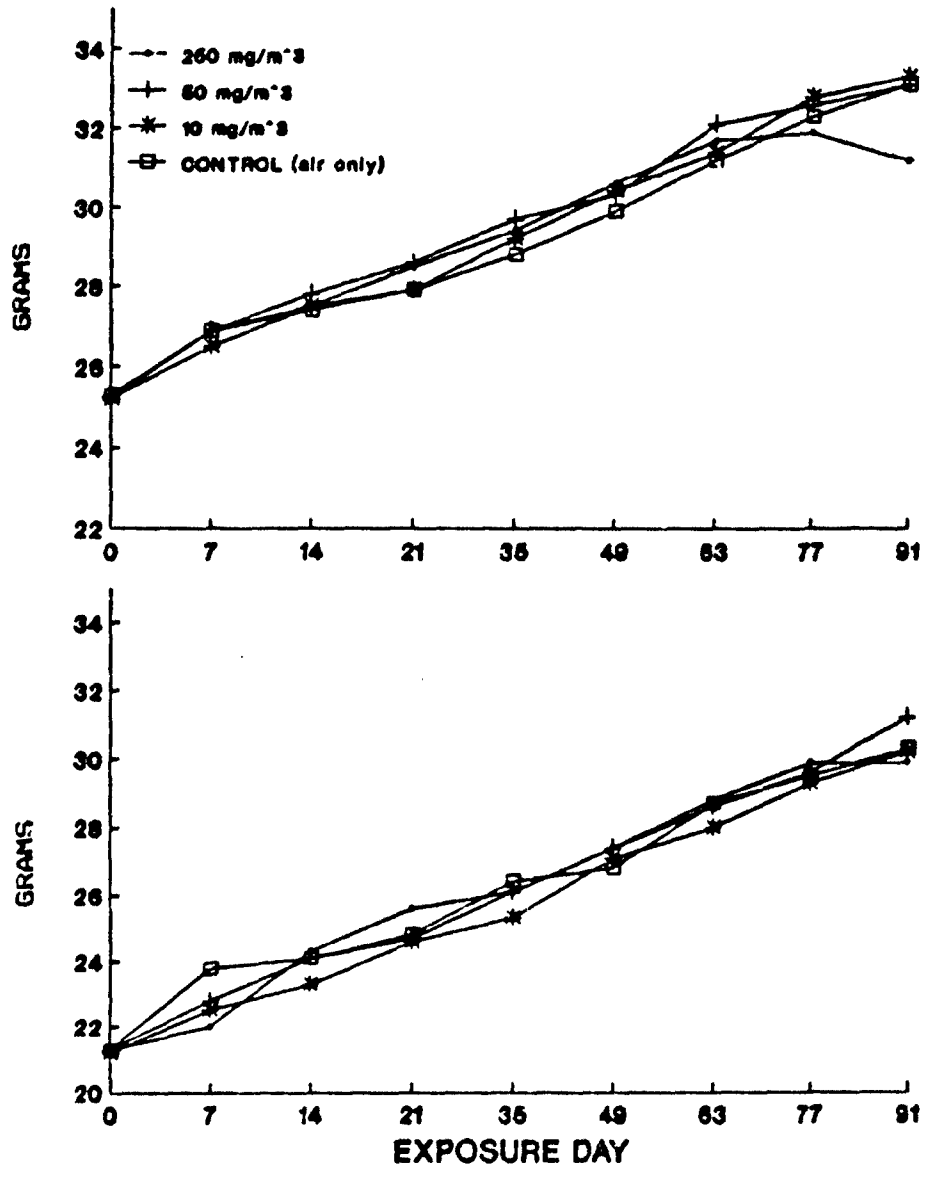

Figure 3. Effect of 13-Week CPFB Inhalation Exposure on Mean Body Weights of B6C3F1 Male (above) and Female Mice (N = 12). There were no statistical differences between treatment groups and controls.

Blood chemistry data from these animals are listed in Tables 6 through 9. Alkaline phosphatase values were significantly ($p<0.01$) increased in both male and female mice exposed to 250 mg CPFB/m^3. Male mice exposed at 50 mg CPFB/m^3 and female mice exposed at 10 mg CPFB/m^3 also had an increase in this enzyme. All other parameters were within normal limits.

TABLE 6. MEAN[a] SERUM CHEMISTRY PARAMETERS FOR MALE F-344 RATS FOLLOWING 13-WEEK REPEATED INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
Glucose (mg/dL)	128.6 ± 6.2	124.4 ± 6.0	124.4 ± 4.8	122.3 ± 6.6
Urea nitrogen (mg/dL)	12.0 ± 0.5	12.2 ± 0.7	13.2 ± 0.2	12.7 ± 0.5
Creatinine (mg/dL)	0.3 ± <0.1	0.4 ± <0.1	0.3 ± <0.1	0.4 ± <0.1
Sodium (mmol/L)	145.0 ± 0.3	145.4 ± 0.2	145.8 ± 0.4	145.6 ± 0.5
Potassium (mmol/L)	5.2 ± 0.1	5.0 ± 0.2	5.1 ± 0.1	5.1 ± 0.1
Chloride (mmol/L)	101.1 ± 0.7	101.0 ± 0.7	102.5 ± 0.6	101.2 ± 0.9
Calcium (mg/dL)	10.7 ± 0.1	10.8 ± 0.1	10.8 ± 0.1	10.9 ± 0.1
Phosphorus (mg/dL)	8.3 ± 0.2	7.8 ± 0.2	8.3 ± <0.1	8.6 ± 0.2
Cholesterol (mg/dL)	45.0 ± <0.1	45.1 ± <0.1	45.0 ± <0.1	46.3 ± 1.3
Total protein (g/dL)	6.1 ± 0.1	6.2 ± 0.1	6.2 ± 0.1	6.4 ± 0.1
Albumin (g/dL)	3.3 ± 0.1	3.4 ± 0.1	3.4 ± 0.1	3.5 ± <0.1
SGOT/AST (IU/L)	127.0 ± 8.9	124.6 ± 10.7	129.1 ± 7.3	120.9 ± 6.0
SGPT/ALT (IU/L)	67.5 ± 3.6	63.4 ± 2.6	67.4 ± 2.6	57.6 ± 2.4
Alkaline phosphatase (IU/L)	108.0 ± 3.1	103.0 ± 4.3	104.9 ± 13.7	108.8 ± 3.6

[a] Mean ± standard error of the mean (SEM), N = 8.

TABLE 7. MEAN[a] SERUM CHEMISTRY PARAMETERS FOR FEMALE F-344 RATS FOLLOWING 13-WEEK REPEATED INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
Glucose (mg/dL)	109.9 ± 5.0	95.5 ± 4.5	105.4 ± 2.7	105.0 ± 6.4
Urea nitrogen (mg/dL)	15.4 ± 0.8	14.6 ± 0.5	13.9 ± 0.7	16.1 ± 0.9
Creatinine (mg/dL)	0.4 ± <0.1	0.4 ± <0.1	0.3 ± <0.1	0.4 ± <0.1
Sodium (mmol/L)	144.5 ± 0.3	143.4 ± 0.5	144.9 ± 0.3	143.8 ± 0.4
Potassium (mmol/L)	5.1 ± 0.1	5.3 ± 0.2	5.0 ± 0.1	5.0 ± 0.1
Chloride (mmol/L)	101.7 ± 0.1	100.2 ± 0.5	100.6 ± 0.6	100.3 ± 0.5
Calcium (mg/dL)	10.9 ± 0.1	11.0 ± 0.1	10.9 ± 0.1	11.0 ± 0.1
Phosphorus (mg/dL)	7.7 ± 0.4	8.2 ± 0.3	7.9 ± 0.3	7.2 ± 0.3
Total protein (g/dL)	6.4 ± 0.2	6.3 ± 0.1	6.3 ± 0.1	6.5 ± 0.1
Albumin (g/dL)	3.5 ± 0.1	3.5 ± 0.1	3.5 ± 0.1	3.6 ± 0.1
SGOT/AST (IU/L)	110.0 ± 5.6	103.6 ± 6.6	99.4 ± 3.9	101.3 ± 3.9
SGPT/ALT (IU/L)	56.5 ± 4.3	50.4 ± 2.8	50.1 ± 1.3	50.8 ± 2.1
Alkaline phosphatase (IU/L)	89.8 ± 6.8	85.6 ± 4.1	89.4 ± 3.0	80.0 ± 4.3

[a] Mean ± SEM, N = 8.

TABLE 8. MEAN[a] SERUM CHEMISTRY PARAMETERS FOR MALE B6C3F1 MICE FOLLOWING 13-WEEK REPEATED INHALATION EXPOSURE TO CPFB

Parameter	Control (8)[b]	10 mg/m³ (6)[b]	50 mg/m³ (8)[b]	250 mg/m³ (6)[b]
Urea nitrogen (mg/dL)	28.0 ± 14.1	16.3 ± 1.4	17.8 ± 1.8	12.3 ± 0.8
Creatinine (mg/dL)	0.1 ± <0.1	0.1 ± <0.1	0.1 ± <0.1	0.1 ± <0.1
SGOT/AST (IU/L)	337.9 ± 96.2[c]	195.9 ± 84.2	278.9 ± 53.5	260.3 ± 66.8
SGPT/ALT (IU/L)	342.0 ± 88.6	118.9 ± 60.7	378.6 ± 111.1	314.5 ± 97.5
Alkaline phosphatase (IU/L)	76.9 ± 6.1	75.8 ± 5.2	109.5 ± 4.3[d]	98.0 ± 3.6[d]

[a] Mean ± SEM, (N).
[b] Number of animals exposed.
[c] N = 7.
[d] Significantly different from controls at $p < 0.01$, as determined by a two-factorial analysis of variance with multivariate comparisons.

TABLE 9. MEAN[a] SERUM CHEMISTRY PARAMETERS FOR FEMALE B6C3F1 MICE FOLLOWING 13-WEEK REPEATED INHALATION EXPOSURE TO CPFB

Parameter	Control (8)[b]	10 mg/m³ (6)[b]	50 mg/m³ (8)[b]	250 mg/m³ (8)[b]
Urea nitrogen (mg/dL)	16.5 ± 1.1	15.7 ± 1.0	21.5 ± 4.9	16.1 ± 1.8
Creatinine (mg/dL)	0.1 ± <0.1	0.1 ± <0.1	0.1 ± 0.1	0.1 ± 0.1
SGOT/AST (IU/L)	82.6 ± 12.9	99.3 ± 17.5	85.0 ± 9.3	84.8 ± 17.4
SGPT/ALT (IU/L)	28.1 ± 3.5	33.3 ± 3.6	30.6 ± 3.8	22.8 ± 6.4
Alkaline phosphatase (IU/L)	118.6 ± 7.8	127.2 ± 4.4	121.3 ± 5.0	147.8 ± 8.2[c]

[a] Mean ± SEM, (N).
[b] Number of animals exposed.
[c] Significantly different from controls at $p < 0.01$, as determined by a two-factorial analysis of variance with multivariate comparisons.

No concentration-related differences in relative organ weights occurred in either rats or mice exposed to CPFB (Tables 10 through 13) sacrificed at the conclusion of the 13-week study. An increase in relative liver weight of the 50-mg CPFB/m³ male mouse group was noted; however, no increase occurred in the relative liver weights of male mice exposed at five times that concentration.

TABLE 10. ORGAN WEIGHTS (g)[a] AND ORGAN-TO-BODY WEIGHT RATIOS (%) OF MALE F-344 RATS FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
Kidney	1.81 ± 0.05	1.87 ± 0.03	1.87 ± 0.05	1.89 ± 0.02
Ratio	0.64 ± 0.01	0.64 ± 0.01	0.71 ± 0.05	0.67 ± <0.01
Heart	0.91 ± 0.01	0.92 ± 0.02	0.88 ± 0.03	0.89 ± 0.02
Ratio	0.32 ± 0.01	0.31 ± 0.01	0.34 ± 0.03	0.32 ± 0.01
Brain	1.86 ± 0.06	1.80 ± 0.02	1.78 ± 0.03	1.75 ± 0.02
Ratio	0.66 ± 0.03	0.62 ± 0.02	0.68 ± 0.06	0.62 ± 0.01
Liver	7.19 ± 0.23	7.56 ± 0.23	7.51 ± 0.25	7.69 ± 0.14
Ratio	2.52 ± 0.02	2.58 ± 0.03	2.84 ± 0.19	2.74 ± 0.03
Spleen	0.58 ± 0.02	0.60 ± 0.01	0.58 ± 0.01	0.56 ± <0.01
Ratio	0.20 ± <0.01	0.21 ± 0.01	0.22 ± 0.02	0.20 ± <0.01
Thymus	0.31 ± 0.03	0.27 ± 0.01	0.31 ± 0.02	0.28 ± 0.02
Ratio	0.11 ± 0.01	0.09 ± <0.01	0.12 ± 0.01	0.10 ± 0.01
Lungs	1.62 ± 0.05	1.77 ± 0.06	1.65 ± 0.06	1.61 ± 0.06
Ratio	0.57 ± 0.02	0.61 ± 0.02	0.63 ± 0.04	0.57 ± 0.02
Adrenals	0.04 ± <0.01	0.05 ± <0.01	0.05 ± <0.01	0.05 ± <0.01
Ratio	0.02 ± <0.01	0.02 ± <0.01	0.02 ± <0.01	0.02 ± <0.01
Testes	2.97 ± 0.05	2.92 ± 0.04	2.92 ± 0.04	2.91 ± 0.04
Ratio	1.05 ± 0.02	1.00 ± 0.01	1.11 ± 0.10	1.04 ± 0.02
Whole Body[b]	285.1 ± 7.7	292.7 ± 7.1	272.8 ± 18.1	281.2 ± 3.0

a Mean ± SEM, N = 8.
b Fasted weight.

TABLE 11. ORGAN WEIGHTS (g)[a] AND ORGAN-TO-BODY WEIGHT RATIOS (%) OF FEMALE F-344 RATS FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m³	50 mg/m³	250 mg/m³
Kidney	1.18 ± 0.02	1.14 ± 0.01	1.17 ± 0.02	1.17 ± 0.02
Ratio	0.68 ± 0.01	0.69 ± 0.01	0.70 ± 0.01	0.69 ± 0.02
Heart	0.64 ± 0.01	0.59 ± 0.01	0.64 ± 0.02	0.62 ± 0.02
Ratio	0.37 ± 0.01	0.36 ± 0.01	0.38 ± 0.01	0.37 ± 0.01
Brain	1.74 ± 0.02	1.75 ± 0.01	1.72 ± 0.02	1.72 ± 0.03
Ratio	1.01 ± 0.01	1.06 ± 0.02	1.03 ± 0.02	1.01 ± 0.01
Liver	4.61 ± 0.12	4.41 ± 0.11	4.44 ± 0.12	4.69 ± 0.05
Ratio	2.67 ± 0.05	2.66 ± 0.04	2.65 ± 0.02	2.76 ± 0.04
Spleen	0.43 ± 0.01	0.42 ± 0.01	0.41 ± 0.02	0.40 ± 0.01
Ratio	0.25 ± 0.01	0.25 ± 0.01	0.24 ± 0.01	0.24 ± <0.01
Thymus	0.23 ± 0.01	0.21 ± 0.01	0.22 ± 0.25	0.23 ± 0.01
Ratio	0.13 ± 0.01	0.12 ± 0.01	0.13 ± 0.01	0.14 ± 0.01
Lungs	1.20 ± 0.04	1.30 ± 0.03	1.27 ± 0.02	1.30 ± 0.04[b]
Ratio	0.69 ± 0.02	0.79 ± 0.02	0.76 ± 0.02	0.76 ± 0.02[b]
Adrenals	0.06 ± <0.01	0.05 ± <0.01	0.06 ± <0.01	0.05 ± <0.01
Ratio	0.03 ± <0.01	0.03 ± <0.01	0.03 ± <0.01	0.03 ± <0.01
Ovaries	0.11 ± 0.01	0.10 ± <0.01	0.10 ± 0.01	0.10 ± <0.01
Ratio	0.07 ± 0.01	0.06 ± <0.01	0.06 ± <0.01	0.06 ± <0.01
Whole Body[c]	172.9 ± 3.1	165.9 ± 2.7	167.7 ± 4.3	169.9 ± 3.0

[a] Mean ± SEM, N = 8.
[b] N = 7.
[c] Fasted weight.

TABLE 12. ORGAN WEIGHTS (g)[a] AND ORGAN-TO-BODY WEIGHT RATIOS (%) OF MALE B6C3F1 MICE FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3[b]
Kidney	0.57 ± 0.01	0.61 ± 0.01	0.56 ± 0.01	0.56 ± 0.02
Ratio	1.91 ± 0.06	1.92 ± 0.04	1.88 ± 0.04	1.86 ± 0.04
Heart	0.16 ± <0.01	0.18 ± <0.01[c]	0.16 ± <0.01	0.17 ± <0.01
Ratio	0.54 ± 0.02	0.57 ± 0.02	0.54 ± 0.01	0.56 ± 0.01
Brain	0.44 ± 0.01	0.45 ± 0.01	0.44 ± 0.01	0.45 ± 0.01
Ratio	1.48 ± 0.06	1.53 ± 0.04	1.48 ± 0.05	1.42 ± 0.05
Liver	1.32 ± 0.03	1.46 ± 0.05	1.96 ± 0.04[c]	1.38 ± 0.03
Ratio	4.40 ± 0.07	4.57 ± 0.19	6.57 ± 0.15[c]	4.67 ± 0.11
Spleen	0.07 ± 0.01	0.08 ± <0.01	0.07 ± <0.01	0.07 ± <0.01
Ratio	0.23 ± 0.02	0.24 ± 0.02	0.25 ± 0.01	0.24 ± 0.02
Thymus	0.04 ± <0.01	0.03 ± <0.01	0.03 ± <0.01	0.04 ± <0.01
Ratio	0.12 ± 0.01	0.11 ± 0.01	0.11 ± 0.01	0.13 ± 0.01
Lungs	0.28 ± 0.01	0.30 ± 0.01	0.28 ± 0.01	0.28 ± 0.01
Ratio	0.95 ± 0.05	0.94 ± 0.04	0.94 ± 0.05	0.96 ± 0.03
Adrenals	0.01 ± <0.01	0.01 ± <0.01	0.01 ± <0.01	0.01 ± <0.01
Ratio	0.03 ± <0.01	0.04 ± <0.01	0.03 ± <0.01	0.03 ± 0.01
Testes	0.23 ± 0.01	0.22 ± 0.02	0.24 ± <0.01	0.24 ± 0.01
Ratio	0.77 ± 0.03	0.69 ± 0.09	0.81 ± 0.03	0.83 ± 0.03
Whole Body[d]	30.0 ± 0.8	31.8 ± 0.5	29.8 ± 0.7	29.2 ± 0.5

[a] Mean ± SEM, N = 8.
[b] N = 6.
[c] Significantly different from controls at $p < 0.01$ level, as determined by a two-factorial analysis of variance with multivariate comparisons.
[d] Fasted weight.

TABLE 13. ORGAN WEIGHTS (g)[a] AND ORGAN-TO-BODY WEIGHT RATIOS (%) OF FEMALE B6C3F1 MICE FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

	Control	10 mg/m³ [b]	50 mg/m³	250 mg/m³
Kidney	0.44 ± 0.02	0.42 ± 0.01	0.41 ± 0.01	0.41 ± 0.02
Ratio	1.53 ± 0.05	1.53 ± 0.06	1.48 ± 0.05	1.51 ± 0.07
Heart	0.15 ± <0.01	0.15 ± <0.01	0.15 ± <0.01	0.16 ± 0.01[c]
Ratio	0.54 ± 0.02	0.54 ± 0.02	0.54 ± 0.02	0.59 ± 0.02
Brain	0.50 ± 0.01	0.48 ± 0.01	0.48 ± 0.01	0.48 ± 0.01
Ratio	1.76 ± 0.05	1.75 ± 0.09	1.75 ± 0.08	1.76 ± 0.08
Liver	1.28 ± 0.03	1.28 ± 0.06	1.32 ± 0.05	1.34 ± 0.05
Ratio	4.51 ± 0.10	4.61 ± 0.12	4.79 ± 0.15	4.91 ± 0.16
Spleen	0.10 ± 0.01	0.10 ± <0.01	0.09 ± <0.01	0.10 ± 0.01
Ratio	0.34 ± 0.02	0.35 ± 0.02	0.34 ± 0.02	0.37 ± 0.02
Thymus	0.05 ± <0.01	0.05 ± <0.01	0.05 ± <0.01	0.06 ± <0.01
Ratio	0.18 ± 0.01	0.19 ± 0.02	0.19 ± 0.02	0.20 ± 0.02
Lungs	0.27 ± 0.01	0.28 ± 0.01	0.27 ± 0.01	0.28 ± 0.01
Ratio	0.94 ± 0.03	1.03 ± 0.04	1.00 ± 0.03	1.03 ± 0.04
Adrenals	0.02 ± <0.01	0.01 ± <0.01	0.01 ± <0.01	0.01 ± <0.01
Ratio	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01	0.05 ± 0.01
Ovaries	0.03 ± <0.01	0.03 ± <0.01	0.03 ± <0.01	0.02 ± <0.01
Ratio	0.10 ± 0.01	0.10 ± 0.01	0.09 ± 0.01	0.08 ± 0.01
Whole Body[d]	28.5 ± 0.5	27.7 ± 0.9	27.7 ± 0.8	27.4 ± 0.8

[a] Mean ± SEM, N = 8.
[b] N = 7.
[c] Significantly different from controls at $p<0.01$ level, as determined by a two-factorial analysis of variance with multivariate comparisons.
[d] Fasted weight.

Treated mice held postexposure gained weight at a rate consistent to that of the control mice during the six-month period (Appendix E and F). Blood chemistry assays performed on the mice postexposure were all within normal limits (Tables 14 and 15). Organ weights measured at necropsy showed no treatment-related differences in either sex (Tables 16 and 17).

Microscopic examination of specimens taken from all study animals did not reveal any treatment-related lesions. Lesions noted were considered to be nonsignificant, spontaneous findings not related to exposure.

TABLE 14. MEAN[a] SERUM CHEMISTRY PARAMETERS FOR MALE B6C3F1 MICE SIX MONTHS FOLLOWING 13-WEEK REPEATED INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
Urea nitrogen (mg/dL)	19.8 ± 0.7	18.5 ± 2.9	19.2 ± 1.7	18.5 ± 1.0
Creatinine (mg/dL)	0.1 ± <0.1	0.1 ± <0.1	0.1 ± <0.1	0.1 ± <0.1[b]
SGOT/AST (IU/L)	45.8 ± 15.9	62.0 ± 5.5	66.3 ± 4.6	57.5 ± 3.6
SGPT/ALT (IU/L)	28.3 ± 14.2	13.3 ± 7.1	25.3 ± 8.6	28.0 ± 4.9
Alkaline phosphatase (IU/L)	182.3 ± 65.6	91.3 ± 15.9	85.3 ± 7.2	82.0 ± 4.8

[a] Mean ± SEM, N = 4.
[b] N = 3.

TABLE 15. MEAN[a] SERUM CHEMISTRY PARAMETERS FOR FEMALE B6C3F1 MICE SIX MONTHS FOLLOWING 13-WEEK REPEATED INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m^3	50 mg/m^{3b}	250 mg/m^{3b}
Urea nitrogen (mg/dL)	13.4 ± 2.1	14.1 ± 1.3	11.9 ± 0.2	12.4 ± 0.5
Creatinine (mg/dL)	0.1 ± <0.1	0.1 ± <0.1	0.1 ± <0.1	0.1 ± <0.1
SGOT/AST (IU/L)	44.7 ± 13.9	57.5 ± 3.9	62.3 ± 4.3	65.7 ± 0.3
SGPT/ALT (IU/L)	19.5 ± 5.5[c]	21.8 ± 6.4	14.7 ± 5.2	20.7 ± 1.5
Alkaline phosphatase (IU/L)	253.3 ± 92.4	160.3 ± 20.4	173.0 ± 17.6	181.7 ± 21.3

[a] Mean ± SEM, N = 4.
[b] N = 3.
[c] N = 2.

TABLE 16. ORGAN WEIGHTS (g) AND ORGAN-TO-BODY WEIGHT RATIOS (%) OF MALE B6C3F1 MICE SIX MONTHS FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3[b]
Kidney	0.72 ± 0.02	0.69 ± 0.03	0.72 ± 0.03	0.70 ± 0.04
Ratio	1.68 ± 0.10	1.78 ± 0.17	1.73 ± 0.03	1.71 ± 0.10
Heart	0.21 ± 0.01	0.20 ± 0.02	0.20 ± 0.01	0.20 ± 0.01
Ratio	0.48 ± 0.01	0.51 ± 0.02	0.48 ± 0.02	0.49 ± 0.01
Brain	0.45 ± 0.01	0.45 ± 0.03	0.45 ± 0.01	0.45 ± 0.01
Ratio	1.04 ± 0.05	1.15 ± 0.11	1.09 ± 0.04	1.10 ± 0.03
Liver	1.71 ± 0.10	1.51 ± 0.12	1.61 ± 0.12	1.57 ± 0.13
Ratio	3.97 ± 0.11	3.85 ± 0.12	3.89 ± 0.16	3.83 ± 0.18
Spleen	0.08 ± <0.01	0.08 ± 0.01	0.08 ± <0.01	0.07 ± 0.01
Ratio	0.19 ± 0.01	0.19 ± 0.01	0.19 ± 0.01	0.17 ± 0.02
Thymus	0.07 ± 0.01	0.08 ± 0.02	0.06 ± 0.02	0.06 ± 0.01
Ratio	0.16 ± 0.02	0.20 ± 0.02	0.14 ± 0.04	0.14 ± 0.02
Lungs	0.30 ± 0.01	0.29 ± 0.02	0.32 ± 0.02	0.32 ± 0.01
Ratio	0.70 ± 0.02	0.73 ± 0.04	0.79 ± 0.05	0.77 ± 0.01
Adrenals	0.01 ± <0.01	0.01 ± <0.01	0.01 ± <0.01	0.01 ± <0.01
Ratio	0.03 ± <0.01	0.03 ± <0.01	0.03 ± <0.01	0.03 ± <0.01
Testes	0.20 ± 0.04	0.23 ± 0.01	0.23 ± 0.01	0.24 ± 0.01
Ratio	0.47 ± 0.10	0.59 ± 0.05	0.55 ± 0.02	0.58 ± 0.01
Whole Body[c]	43.0 ± 1.4	39.4 ± 3.0	41.3 ± 1.4	40.8 ± 1.6

[a] Mean ± SEM, N = 4.
[b] N = 3.
[c] Fasted weight.

TABLE 17. ORGAN WEIGHTS (g)[a] AND ORGAN-TO-BODY WEIGHT RATIOS (%) OF FEMALE B6C3F1 MICE SIX MONTHS FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

Parameter	Control	10 mg/m^3	50 mg/m^3[b]	250 mg/m^3
Kidney	0.47 ± 0.02	0.48 ± 0.03	0.46 ± 0.03	0.45 ± 0.01
Ratio	1.38 ± 0.10	1.27 ± 0.04	1.24 ± 0.04	1.36 ± 0.10
Heart	0.18 ± 0.01	0.17 ± <0.01	0.16 ± 0.01	0.17 ± 0.01
Ratio	0.52 ± 0.04	0.44 ± 0.01	0.43 ± 0.02	0.52 ± 0.04
Brain	0.46 ± 0.01	0.48 ± 0.01	0.46 ± 0.01	0.45 ± 0.01
Ratio	1.38 ± 0.13	1.27 ± 0.03	1.25 ± 0.11	1.39 ± 0.13
Liver	1.41 ± 0.12	1.36 ± 0.05	1.31 ± 0.03	1.31 ± 0.05
Ratio	4.08 ± 0.10	3.58 ± 0.12	3.50 ± 0.13	3.96 ± 0.22
Spleen	0.11 ± 0.01	0.11 ± 0.01	0.10 ± 0.01	0.10 ± 0.01
Ratio	0.33 ± 0.02	0.30 ± 0.05	0.28 ± 0.03	0.29 ± 0.02
Thymus	0.05 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.05 ± 0.02
Ratio	0.15 ± 0.02	0.13 ± 0.02	0.15 ± 0.01	0.14 ± 0.04
Lungs	0.33 ± 0.03	0.33 ± 0.01	0.28 ± 0.01[c]	0.30 ± 0.01
Ratio	0.96 ± 0.02	0.88 ± 0.04	0.71 ± 0.01	0.90 ± 0.08
Adrenals	0.02 ± <0.01	0.02 ± <0.01	0.02 ± <0.01	0.02 ± <0.01
Ratio	0.04 ± 0.01	0.04 ± 0.01	0.04 ± <0.01	0.05 ± <0.01
Ovaries	0.04 ± 0.01	0.03 ± 0.01	0.02 ± 0.01	0.03 ± 0.01
Ratio	0.13 ± 0.04	0.09 ± 0.02	0.06 ± 0.01	0.08 ± 0.01
Whole Body[d]	34.7 ± 3.7	38.1 ± 1.3	37.6 ± 2.4	33.5 ± 3.0

[a] Mean ± SEM, N = 4
[b] N = 3
[c] N = 2
[d] Fasted weight

SECTION 4

DISCUSSION

Single peroral doses of CPFB to rats at the limit test dose level of 5 g/kg caused mortality in one of five male rats and two of five female rats. These results indicate an LD_{50} greater than 5 g/kg, which would classify the compound as "practically non-toxic" by this route of administration (Deichman and Gerarde, 1969). The oral results are not dissimilar to the other acute toxicity results, which indicate that this compound does not pose an acute toxicological hazard. A summary of CPFB acute toxicity assays is presented in Table 18.

TABLE 18. SUMMARY OF ACUTE TEST RESULTS FOR CPFB

Eye Irritation[a]	Skin Irritation[a]	Sensitization[a]	Oral LD_{50} (g/kg)	Inhalation LC_{50} (mg/L)[a]
Mild	Mild	Negative	>5.0	>4.84

[a] Data from Kinkead et al. (1987).

The only death that occurred during the 13-week inhalation exposure was a female mouse, exposed at the lowest CPFB concentration level, which died following the twenty-ninth exposure day. The cause of death was determined to be leukemia and not related to exposure. Although alkaline phosphatase values were slightly increased in both sexes of mice exposed at the highest concentration level, the differences were not considered physiologically significant because all values were within normal ranges repeated by other investigators (Wolford et al., 1986).

Statistical analysis of the histopathologic results revealed no treatment-related effects as a result of the 13-week inhalation exposure. In the 21-day inhalation study (Kinkead et al., 1990) foci of hepatic single cell necrosis was reported as a significant treatment-related finding at 0.2 mg CPFB/L. This finding was not noted in the histologic results of this study at the same exposure level. Because of the different findings between the two studies, the hepatic tissues of both studies were reviewed. Using incidence defined as present or absent, and a severity scoring system based on relative number of necrotic foci in liver sections, the review disclosed that the finding was present in the original study. However, the slightly increased number of these foci in dosed animals compared to control animals, coupled with a severity that did not exceed minor or very slight, suggests an exposure-induced lesion that is statistically significant, but biologically insignificant.

The concentration of 250 mg CPFB/m^3 is close to the effect threshold at or below which no deleterious sequelae may be expected. Under the conditions of intended use (short-term, repeated basis) individuals should not be allowed to inhale more than 250 mg of CPFB/m^3 for extended periods

of time. It must be emphasized that this "standard" is only an estimate based on experimental data and is subject to modification by data collected from human experience.

SECTION 5

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APPENDICES

APPENDIX A

MEAN[a] BODY WEIGHTS (g) OF MALE RATS DURING 13-WEEK INHALATION EXPOSURE TO CPFB

Day	Control	10 mg/m³	50 mg/m³	250 mg/m³
0	175.9 ± 2.7	175.5 ± 2.8	175.8 ± 2.6	176.6 ± 2.3
8	198.7 ± 3.4	197.6 ± 3.6	198.9 ± 3.3	202.4 ± 2.8
15	208.f ± 4.4	209.0 ± 4.0	208.6 ± 3.5	212.0 ± 3.8
22	224.. ± 4.8	224.2 ± 4.1	223.2 ± 4.3	224.8 ± 3.4
36	244.8 ± 5.2	248.3 ± 5.5	245.6 ± 4.4	249.3 ± 3.3
50	264.6 ± 6.1	269.1 ± 5.1	263.9 ± 5.3	266.4 ± 4.0
64	276.5 ± 7.0	281.9 ± 5.9	276.0 ± 6.4	279.8 ± 4.0
78	288.5 ± 7.8	296.6 ± 6.4	288.5 ± 7.1	292.7 ± 3.9
92	296.1 ± 8.0	305.2 ± 6.9	296.4 ± 7.6	295.5 ± 3.4

[a] Mean ± SEM, N = 8.

APPENDIX B

MEAN[a] BODY WEIGHTS (g) OF FEMALE RATS DURING 13-WEEK INHALATION EXPOSURE TO CPFB

Day	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
0	132.2 ± 1.3	131.9 ± 1.4	131.8 ± 1.2	132.5 ± 1.2
8	143.0 ± 1.4	140.8 ± 1.7	138.9 ± 1.4	139.5 ± 1.4
15	148.4 ± 2.0	144.8 ± 1.7	143.7 ± 2.1	143.7 ± 1.8
22	151.8 ± 1.7	149.3 ± 2.2	148.3 ± 2.2	150.1 ± 1.3
36	160.2 ± 3.0	154.2 ± 2.4	154.4 ± 3.2	158.0 ± 2.1
50	169.1 ± 3.1	160.8 ± 2.6	162.2 ± 4.0	163.8 ± 3.0
64	175.2 ± 3.0	167.4 ± 2.8	165.9 ± 3.9	170.5 ± 3.1
78	177.9 ± 2.9	172.1 ± 3.0	171.4 ± 4.5	174.2 ± 2.9
92	181.5 ± 3.1	173.0 ± 2.9	173.9 ± 4.8	177.4 ± 2.8

[a] Mean ± SEM, N = 8.

APPENDIX C

MEAN• BODY WEIGHTS (g) OF MALE B6C3F1 MICE DURING 13-WEEK INHALATION EXPOSURE TO CPFB

Day	Control	10 mg/m³	50 mg/m³	250 mg/m³
0	25.3 ± 0.4	25.2 ± 0.4	25.3 ± 0.4	25.2 ± 0.4
7	26.9 ± 0.3	26.5 ± 0.3	26.9 ± 0.5	26.9 ± 0.3
14	27.4 ± 0.3	27.5 ± 0.3	27.8 ± 0.6	27.5 ± 0.4
21	27.9 ± 0.4	27.9 ± 0.3	28.6 ± 0.6	28.5 ± 0.3
35	28.8 ± 0.4	29.2 ± 0.3	29.7 ± 0.6	29.4 ± 0.4
49	29.9 ± 0.5	30.4 ± 0.4	30.3 ± 0.5	30.6 ± 0.4
63	31.2 ± 0.5	31.4 ± 0.4	32.1 ± 0.5	31.7 ± 0.5
77	32.3 ± 0.5	32.8 ± 0.4	32.6 ± 0.5	31.9 ± 0.5
91	33.1 ± 0.5	33.3 ± 0.4	33:1 ± 0.6	31.2 ± 0.5

• Mean ± SEM, N = 12.

APPENDIX D

MEAN[a] BODY WEIGHTS (g) OF FEMALE B6C3F1 MICE DURING 13-WEEK INHALATION EXPOSURE TO CPFB

Day	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
0	21.3 ± 0.3	21.2 ± 0.3	21.3 ± 0.3	21.3 ± 0.3
7	23.8 ± 1.1	22.5 ± 0.4	22.8 ± 0.4	22.0 ± 0.5
14	24.1 ± 0.3	23.3 ± 0.3	24.1 ± 0.5	24.3 ± 0.3
21	24.8 ± 0.3	24.6 ± 0.2	24.7 ± 0.5	25.6 ± 0.4
35	26.4 ± 0.3	25.3 ± 0.5	26.1 ± 0.4	26.1 ± 0.3
49	26.8 ± 0.3	27.1 ± 0.5[b]	27.4 ± 0.5	27.4 ± 0.4
63	28.7 ± 0.4	28.0 ± 0.4[b]	28.6 ± 0.7	28.8 ± 0.5
77	29.5 ± 0.4	29.3 ± 0.6[b]	29.6 ± 0.3	29.9 ± 0.5
91	30.3 ± 0.4	30.2 ± 0.5[b]	31.2 ± 0.8	29.9 ± 0.5

[a] Mean ± SEM, N = 12.
[b] N = 11.

APPENDIX E

MEAN[a] BODY WEIGHTS (g) OF MALE B6C3F1 MICE HELD 6 MONTHS POSTEXPOSURE FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

Postexposure Month	Control	10 mg/m^3	50 mg/m^3	250 mg/m^3
1	37.5 ± 0.4	34.0 ± 1.2	36.0 ± 1.4	33.8 ± 1.5
2	39.3 ± 1.6	36.9 ± 1.0	39.8 ± 1.7	36.6 ± 1.3
3	44.8 ± 1.7	40.8 ± 1.7	42.3 ± 2.1	40.1 ± 1.5
4	45.4 ± 2.0	42.2 ± 1.9	44.7 ± 1.5	41.7 ± 2.0
5	46.6 ± 1.5	42.7 ± 2.6	45.0 ± 1.6	42.6 ± 1.7
6	47.4 ± 1.7	43.4 ± 3.4[b]	45.6 ± 1.6	44.2 ± 1.3

[a] Mean ± SEM, N = 4.
[b] N = 3.

APPENDIX F

MEAN[a] BODY WEIGHTS (g) OF FEMALE B6C3F1 MICE HELD SIX MONTHS POSTEXPOSURE FOLLOWING 13-WEEK INHALATION EXPOSURE TO CPFB

Postexposure Month	Control	10 mg/m^3	50 mg/m^3[b]	250 mg/m^3
1	31.9 ± 1.1	34.2 ± 1.0	33.2 ± 1.6	30.6 ± 1.7
2	35.6 ± 1.8	39.2 ± 0.6	37.6 ± 2.9	34.7 ± 2.2
3	35.1 ± 2.7	39.9 ± 1.0	37.5 ± 1.3	34.0 ± 2.7
4	36.0 ± 3.0	41.7 ± 0.7	39.2 ± 1.6	36.8 ± 1.4
5	35.5 ± 3.4	39.8 ± 2.0	39.2 ± 2.7	37.0 ± 2.9
6	36.9 ± 3.4	39.4 ± 1.4	38.9 ± 2.5	35.9 ± 3.4

[a] Mean ± SEM, N = 4.
[b] N = 3.

QUALITY ASSURANCE

The study, "Effects of a 13-Week Chloropentafluorobenzene Inhalation Exposure of Fischer 344 Rats and B6C3F1 Mice," was conducted by the NSI Technology Services Corporation, Toxic Hazards Research Unit under the guidance of the Environmental Protection Agency's Good Laboratory Practices Guidelines, 40CFR PART 792. No claim will be made that this was a "GLP" study as no attempt was made to adhere to the strict requirements of these guidelines. The various phases of this study were inspected by members of the Quality Assurance Unit. Results of these inspections were reported directly to the Study Director at the close of each inspection.

DATE OF INSPECTION:	ITEM INSPECTED:
May 8, 1989	Weigh, randomize male rats.
May 9, 1989	Initiate 90-day exposure.
May 11, 1989	Weigh, randomize female mice, GC calibration check.
May 16, 1989	Miran calibration check.
May 18, 1989	Rotameter calibration check.
June 7, 1989	GC calibration check, data audit.
June 14, 1989	Weigh rats.
June 15, 1989	Weigh mice.
June 20, 1989	Miran calibration check.
July 11, 1989	Miran calibration check.
July 12, 1989	GC calibration check, weigh rats.
July 13, 1989	Weigh mice.
August 1, 1989	Miran calibration check.
August 2, 1989	GC calibration check.
August 8, 1989	Weigh rats, sacrifice male rats.
August 16, 1989	Animal mortality report.
September 6, 1989	Weigh mice post exposure.
September 25, 1989	Data audit.
November 29, 1989	Weigh mice post exposure.
January 24, 1990	Weigh mice post exposure.
February 6, 1990	Weigh mice post exposure, sacrifice female mice.
November 16-30, 1990	Final report audit.

The Quality Assurance Unit has determined by review process that this report accurately describes those methods and standard operating procedures required by the protocol and that the reported results accurately reflect the raw data obtained during the course of the study. No discrepancies were found that would alter the interpretation presented in this Final Report.

M G Schneider

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Date November 29, 1990

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